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Acid Precipitation:

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16. ABSTRACT

While human health impairment has been attributed to pollution by sulfur dioxide (SO_2), data from inhalation studies in animals show that its oxidation products are more irritating. Population surveys in which suspended sulfate was a co-variant suggest that certain health parameters are associated more strongly with sulfate than with SO_2. Recent work with biological models indicate that the sulfates and sulfuric acid act on the lung through the release of histamine and the degree of release is related to the specific cation present. Attention should be given to sulfates and specific cations in atmospheric monitoring.

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Effects of Sulfur Dioxide and Sulfate Aerosol Particles on Human Health

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There must be a reevaluation of the air pollution that results from the combustion of fossil fuels, write the authors. With regard to health effects, specific attention should be given to the cationic substances associated with the sulfur pollutants. The accumulating evidence of the greater toxicity of sulfuric acid and acid sulfates indicates that attention should not only be devoted to the concentrations of emitted sulfur dioxide, but also to conditions which encourage its oxidation.

Sulfur dioxide is ubiquitous in the air of populated communities. Decrements of human health have been ascribed frequently to sulfur dioxide air pollution on the basis of clinical observation and epidemiological association of health impairments with sulfur dioxide (SO_2) concentrations in atmosphere. Many studies attempting to link human health impairment to air pollution have been conducted in the United Kingdom, Japan, the USA and other countries. The epidemiological literature on this topic is too voluminous to be discussed here in detail and has been the subject of many reviews. It has most recently been considered in a USA Academy of Sciences document (1).

Three categories of human disease appear to be influenced by atmospheres containing sulfur dioxide and associated pollutants. These are: altered pulmonary ventilation and increased prevalence of lower pulmonary disease in children, increased frequency or severity of asthmatic attacks, and increased prevalence of chronic respiratory disease. It is also known that experimental exposure of human volunteers and laboratory animals to sulfur dioxide alters certain pulmonary function tests (2, 3, 4).

The problems of interpretation of the epidemiologic data are complex because few, if any, of the studies are based on accurate aerometric data, but instead rely on such parameters as smoke shade, dust fall, coal consumption, *etc.*, or at best, simply sulfur dioxide. Since other pollutants are associated with sulfur dioxide content of the air and there is insufficient accurate aerometric data to assess them in these studies, it is possible that the health decrements demonstrated may have been the result of exposure to these other agents, rather than to sulfur dioxide alone. Particulate material has been considered either as a prime toxicant or as an interactant in enhancing the reactive properties of sulfur dioxide. However, particulate material is not a single entity but is composed of many agents capable of reacting by virtue of their physical properties or their specific chemical identity. Another factor to be considered is that the sulfur dioxide is a precursor to other, more reactive chemical substances which could contribute to the particulate loading of the atmosphere. While in the past the contribution of sulfur dioxide in this regard has been largely ignored in air monitoring data connected with health studies, it is now known that such oxidation products of sulfur dioxide contribute a significant amount of the total airborne particulate material (1).

From the standpoint of health effects, interest in these airborne products stems from observations on experimental animals which showed that the inclusion of a sodium chloride aerosol with sulfur dioxide increased the reactivity as measured by pulmonary flow resistance in guinea pigs (3). The augmented expiratory flow resistance imparted by the sodium chloride particles suggests that biological reaction is increased by condensation of an acid product of sulfur dioxide on the sodium chloride particles. This line of reasoning is strengthened by the observation that in the sodium chloride/sulfur dioxide interaction system, effect is intensified by an increase in relative humidity of the exposure atmosphere (5). It is also possible to rank the various sulfates and sulfuric acid, according to the alteration of pulmonary flow resistance (6).

In Amdur's studies (6), sulfuric acid, zinc ammonium sulfate, ferric sulfate and ammonium sulfate showed a decreasing order of effectiveness in the induction of increased flow resistance, whereas with ferrous sulfate and manganese sulfate there was little increase over control values.

A confounding aspect in all such particulate studies is the strong inverse relationship between particle size and the elicitation of pulmonary flow resistance as demonstrated by Amdur (6) (Figure 1). However, when the particle size factor is controlled, the influence of the cation is still plainly seen.

In a series of recent human population studies, attempts were made to consider suspended sulfate as part of the aerometric data (7). Evidence that certain health parameters correlated better with suspended sulfate than with sulfur dioxide was reported by Shy *et al* (8) and Chapman *et al* (9). While these epidemiologic observations have not been corroborated, they are consistent with the previously cited observations on animals which show greater irritability from inhaled sulfuric acid and specific sulfates than from sulfur dioxide. In view of the relative differences in acute, experimental airway response to the sulfates and sulfuric acid, it seems pertinent to examine the relative role of the specific cations associated with "sulfate" complex.

ROLE OF CATIONS

Evidence is accumulating to show that the specific cations associated with sulfate are important parameters with respect to increased susceptibility to pulmonary infections where the activity of the corresponding chlorides is as great as the sulfate species itself (Gardner, *et al* (10)). Figure 2 demonstrates the similarity of effect of chlorides and sulfate with the same cation. The importance of the cation has also been

Figure 1. Regression curve demonstrating increased pulmonary resistance as a function of diminishing particle size. Computed from data of Amdur (6).

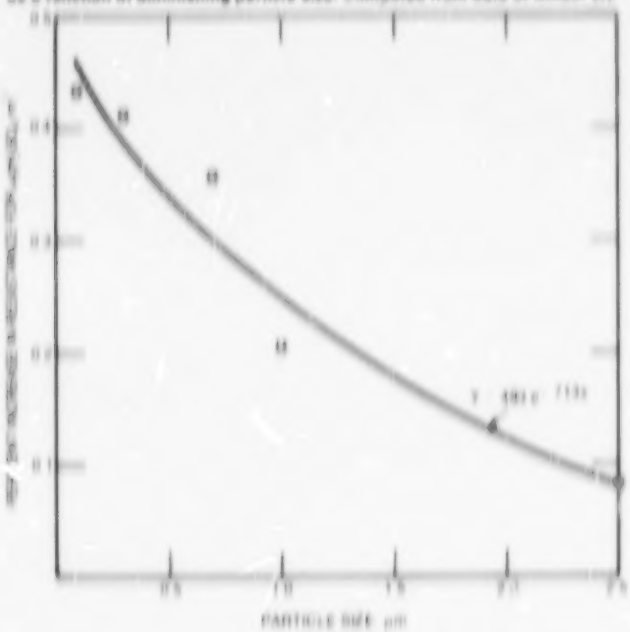


Figure 2. Dose response of mice to bacterial infection of the lung subsequent to exposure to aerosolized cadmium chloride and cadmium sulfate. Data from Gardner *et al* (10).

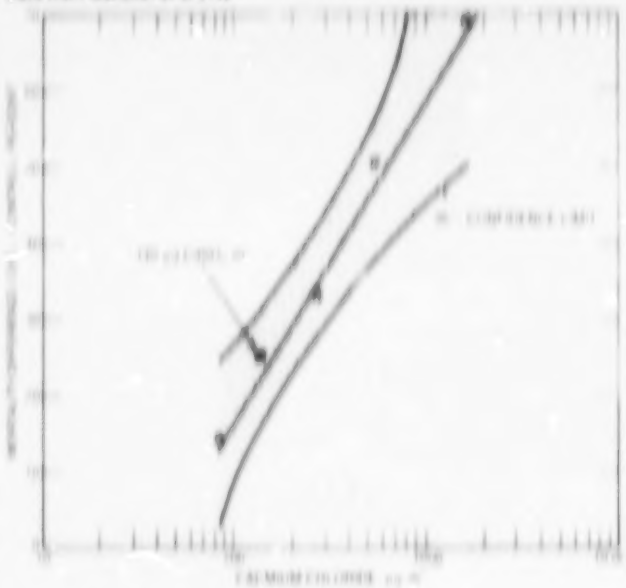
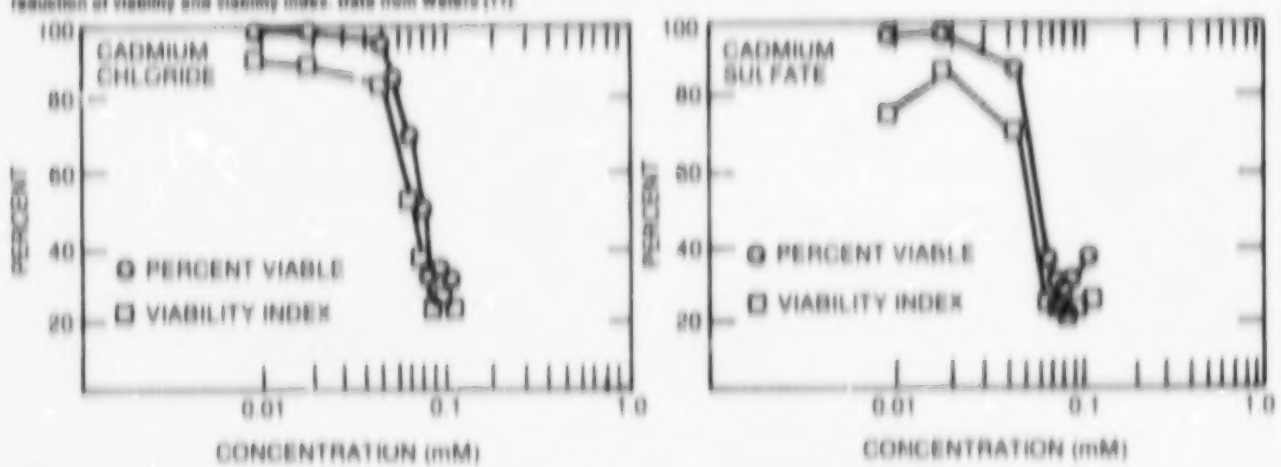


Figure 3. Dose response for *in vitro* exposure of rabbit pulmonary macrophages to cadmium chlorides and cadmium sulfate. Parameters shown are reduction of viability and viability index. Data from Waters (11).



noticed during exposures of isolated fibroblasts and pulmonary macrophages by Waters (11). In these studies the cation has, in general, been the determinant for cell injury. Data showing identical effect for cadmium chlorides and cadmium sulfate are shown in Figure 3.

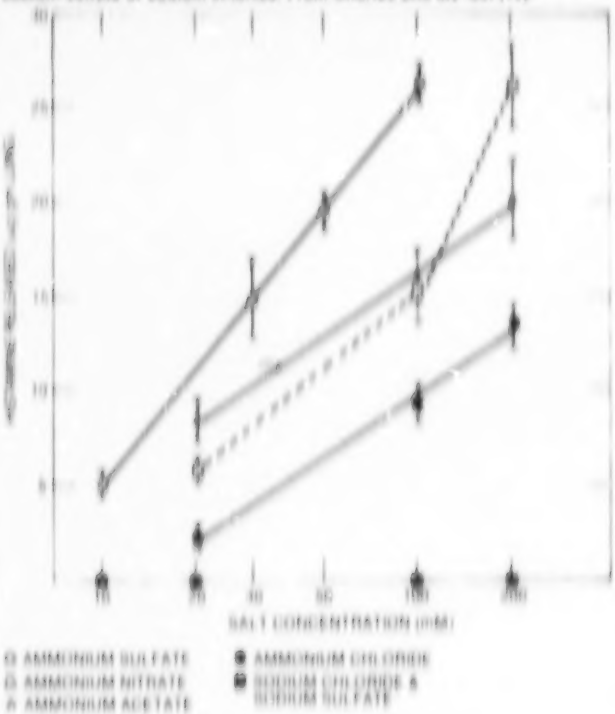
Recent experiments have demonstrated a histamine mediated bronchoconstriction associated with exposure to sulfur compounds. This mechanism appears to be influenced by the absorption and flux of the sulfate ion in the lung. This, too, appears to be related to the effect of the specific cations. Thus, Charles and Menzel (12) noted that when isolated fragments of guinea pig lung were incubated with 10 - 200 mM concentrations of various salts and analyzed for histamines by means of spectrofluorometry, there was a gradation of histamine release according to the specific salt and the concentrations.

Ammonium sulfate was the most potent compound used, releasing 97 percent of the histamine while ammonium nitrite, ammonium acetate and ammonium chloride released 58 percent, 37 percent, and 14 percent, respectively. No histamine was released by sodium chloride or sodium sulfate (Figure 4).

In studies on the isolated perfused rat lung by Charles, Anderson and Menzel (13), Charles (14), bronchoconstriction was produced by intratracheal injections of various salts. Instillations of isotonic sucrose or sodium sulfate produced only minimal response whereas the effect of 1 μ mole of ammonium sulfate was equivalent to 14 μg of histamine. Prior perfusion of the lung with an antihistamine (M mepyramine maleate) blocked the reaction both of histamine and ammonium sulfate (Figure 5). There is a rapid release of histamine, which can be identified in the perfusate. Studies on the isolated perfused lungs also showed that histamine was released after an injection of sulfate salts into the trachea (Figure 6). The reaction both to ammonium sulfate and histamine injection was blocked by prior administration of an antihistamine (mepyramine maleate).

In vivo studies on the lung of a rat by Charles, Gardner, Coffin and Menzel (15) showed a similar response for absorption of sulfate, which was shown to be a nonsaturable process with a half-life of 14.5 minutes which was proportionate to the concentration of the sulfate ion. The process was enhanced by ammonium ions and decreased by chloride ions.

Figure 4. Release of histamine from isolated lung fragments of guinea pig lung after treatment with various salts. Histamine determined spectrofluorometrically. Note that no histamine is released by treatment with sodium sulfate or sodium chloride. From Charles and Menzel (16).



The authors, Charles and Menzel (16) and Charles (14), also indicate that the sulfate removal was differentially enhanced and presumably there was increased flux by various associated cations across the mast cell where histamine is stored. Among the most active in this regard were ferric ions, zinc ions and nickel ions (Figure 7). Furthermore, the absorption of sulfate was also enhanced by either low or high pH (Figure 8). These data correlate with data previously presented by Amdur (3) for pulmonary flow resistance in guinea pigs as related to inhalation exposure to various sulfates and sulfuric acid. Other toxic ions such as cobalt, mercury and cadmium likewise had strong effects on sulfate absorption.

CONCLUSION

It appears significant that the various sulfates can be ranked according to effect in both the classical guinea pig bronchoconstrictive model and in the various recent experiments discussed above in which the release of histamine is measured as an index of effect. The ranking in these two systems is relatively the same when the same compounds are used.

The increasing effect with diminishing particle size might suggest that the deeper the penetration into the airway the greater the reaction. The above possibility is consistent with the postulation that the bronchoconstriction is mediated by the release of histamine which would be more actively triggered in the deeper airways. The data from the infectivity studies and *in vitro* exposures indicate that the various cations have different influences on cellular integrity, which is apparently not modified by the associated anions (at least with respect to sulfate and chloride).

It has been observed that the absorption of sulfate from the lung is also influenced by the associated cation. It would, thus, appear that a possible mechanism of the action of sulfate and probably other compounds such as nitrates is action on the cell membrane by cations which leads to penetration or absorption of the anion into the cell and consequent binding in the mast cell granules with the release of histamine and related substances which initiate the bronchoconstrictive reaction. Such a biochemical mechanism is consistent with accumulating evidence that oxidation products of sulfur dioxide are more irritating than the gas itself.

Figure 5. Effects on respiratory volume of isolated perfused rat lungs from intratracheal infections of various chemicals as compared to isotonic sucrose solution control. Note that little change results from sodium sulfate (A), but that ammonium sulfate or histamine give the same strong response (B). Shown also is the effect of ammonium chloride which is intermediate (C), and blocking action of an antihistaminic drug (mepyramine maleate) (D). From Charles *et al* (15).

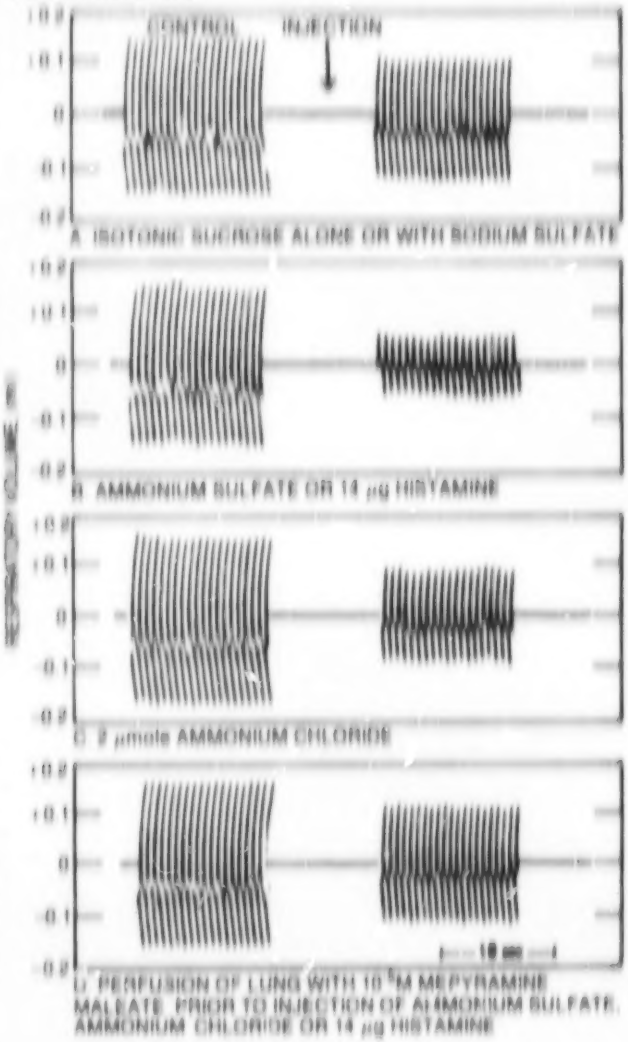

CONTROL
INJECTION
A. ISOTONIC SUCROSE ALONE OR WITH SODIUM SULFATE
B. AMMONIUM SULFATE OR 14 μg HISTAMINE
C. 2 μmole AMMONIUM CHLORIDE
10 sec
D. PERFUSION OF LUNG WITH 10⁻⁵M MEPYRAMINE MALEATE PRIOR TO INJECTION OF AMMONIUM SULFATE, AMMONIUM CHLORIDE OR 14 μg HISTAMINE

Figure 6. Release of histamine into the perfusate of an isolated lung preparation. After injection of ammonium sulfate (arrow) note that the release is rapid after the sulfate exposure. From Charles *et al* (15).

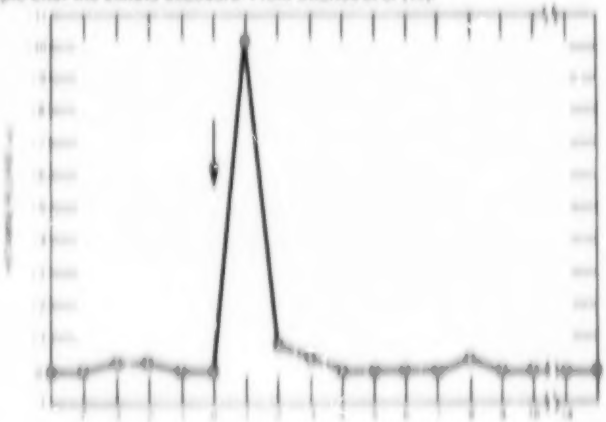


Figure 7. Influence of various sulfates on absorption of sulfate ions from the airway of the rat. Note that the removal of sulfate and presumably the flux across the mast cell is strongly influenced by the cation. Data from Charles et al (16).

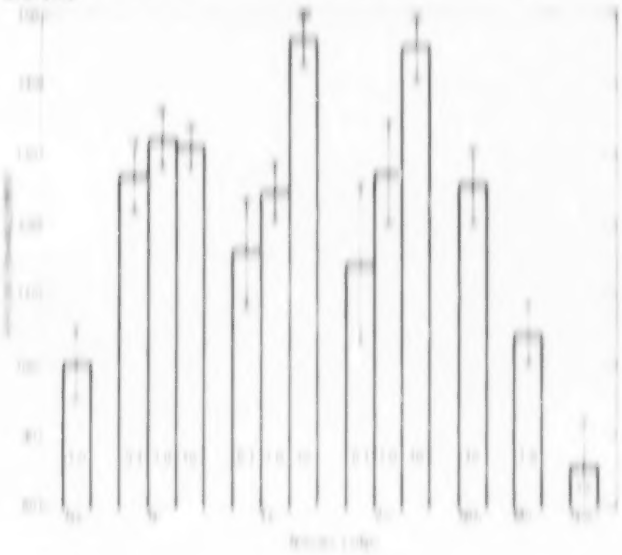
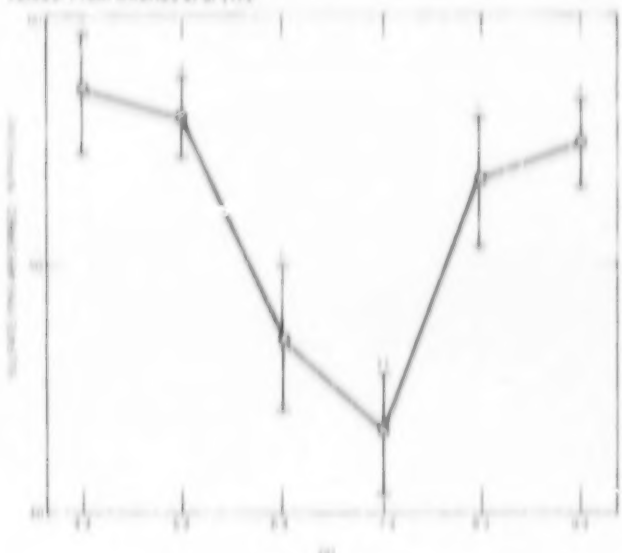


Figure 8. Influence of pH on the absorption of sulfate ions from the airway and the rat lung. Note that absorption is increased at both low and high pH values. From Charles et al (16).



In view of these data, the subject of air pollution stemming from the combustion of fossil fuels from both stationary and mobile sources must be reevaluated. The observations made on biological systems and by population surveys should be extended, with specific attention given to the cationic substance associated with the sulfur pollutants. Where possible, the relative effect of sulfur dioxide, sulfuric acid, and the various sulfates and nitrates determined to be present in polluted air should be investigated in experimental exposure of human volunteers for the purpose of determining dose response in man. The case for greater toxicity of sulfuric acid and acid sulfates indicates that attention should not only be given to the concentration of emitted sulfur dioxide in a given area, but to conditions which encourage its oxidation. Thus, factors such as catalysis and photochemical activity which favor rapid oxidation and which will result in a higher local concentration of sulfate from a given base of sulfur dioxide are important factors in health considerations. Attention should be given to these factors in monitoring and modelling atmospheric air pollution.

References and Note(s)

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